Docket No.: 220316US0PCT

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COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

RE: Application Serial No.: 10/088,090
Applicants: Stephen ARKINSTALL, et al.
Filing Date: June 21, 2002
For: PHARMACEUTICALLY ACTIVE SULFONYL AMINO ACID DERIVATIVES
Group Art Unit: 1625
Examiner: CHANG

SIR:

Attached hereto for filing are the following papers:

Letter to PTO
SUPPLEMENTAL APPEAL BRIEF

Our check in the amount of is attached covering any required fees. In the event any variance exists between the amount enclosed and the Patent Office charges for filing the above-noted documents, including any fees required under 37 C.F.R 1.136 for any necessary Extension of Time to make the filing of the attached documents timely, please charge or credit the difference to our Deposit Account No. 15-0030. Further, if these papers are not considered timely filed, then a petition is hereby made under 37 C.F.R. 1.136 for the necessary extension of time. A duplicate copy of this sheet is enclosed.

Respectfully submitted,

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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF	:
STEPHEN ARKINSTALL, ET AL.	: EXAMINER: CHANG
SERIAL NO: 10/088,090	:
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LETTER TO PTO

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

In response to the Office Communication dated March 15, 2006, Applicants submit herewith an Appeal Brief incorporating the arguments presented in the Reply Brief as required.

Respectfully submitted,

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STEPHEN ARKINSTALL, ET AL.	: EXAMINER: CHANG, CELIA C.
SERIAL NO: 10/088,090	:
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SUPPLEMENTAL APPEAL BRIEF

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

This brief is submitted in response to the rejections dated December 29, 2004.

REAL PARTY OF INTEREST

The real party of interest herein is Applied Research Systems ARS Holding N.V., Curacao, Netherland Antilles.

RELATED APPEALS AND INTERFERENCES

To the best of Appellants' knowledge, there are no other appeals or interferences which will directly affect or be directly affected by, or have a bearing on, the Board's decision in this appeal.

STATUS OF CLAIMS

Claims 1, 7-9, 17-19, 29-35, 38, 39 and 41-45 are active in this application.

STATUS OF AMENDMENTS

There are no outstanding amendments in this case.

SUMMARY OF CLAIMED SUBJECT MATTER

As described in the specification on page 5:

> [I]t is an objective of the present invention to provide relatively small molecules that avoid essentially all of the above-mentioned drawbacks arising from the use of peptides or proteins, however, which are suitable for the treatment of a variety of diseases, in particular of neuronal or the autoimmune system related disorders. It is notably an objective of the present invention to provide relatively small molecule chemical compounds which are able to modulate, preferably down-regulate or to inhibit the JNK (Jun Kinase) pathway so to be available as a convenient method of treating diseases which are preferably mediated by the JNK function.

Further, on page 9 of the specification describes:

> Quite surprisingly, it was now found that sulfonyl amino acid derivatives according to formula I are suitable pharmaceutically active agents, by effectively inhibiting the action of JNKs, notably JNK2 and 3. In terms of application convenience, the inventively found compounds display marked superiority compared to the above mentioned peptide or protein approach as they are also accessible to oral administration. They could

> be prescribed by a physician and require only minor supervision. Also, the inventively found compounds are available at lower costs compared to said peptide compounds described hitherto.

On page 13, line 24 – page 14, line 3 the specification describes:

. . .the compounds pursuant to formula I are useful for the treatment or prevention of immuno- and/or neuronal-related diseases or pathological states in which inhibition of JNK1 and/or JNK2 and/or JNK3 plays a critical role such as epilepsy; neurodegenerative diseases including Alzheimer's disease, Huntington's disease, Parkinson's disease; retinal diseases; spinal cord injury; head trauma, autoimmune diseases including multiple Sclerosis, inflammatory bowel disease (IBD), rheumatoid arthritis; asthma; septic shock; transplant rejection; cancers including breast, colorectal, pancreatic and cardiovascular diseases including stroke, cerebral ischemia, arterosclerosis, myocordial infarction, myocordial reperfusion injury.

ISSUES TO BE REVIEWED ON APPEAL

(1) The first issue to be reviewed on appeal is the rejection Claims 1, 7-8, 17-19, 29-35, and 38-39 under 35 U.S.C. § 112, first paragraph based on the allegation that the claims include new matter.

(2) The issue issued to be reviewed on appeal is the objection of Claims 9 and 29 under 37 CFR 1.75(c) based on the allegation that Claims 9 and 29 fail to further limit the claims from which they depend.

(3) The third issue to be reviewed on appeal is the rejection of Claims 1, 7-8, 17-19, 29-35, 38-39 and 41-45 under 35 U.S.C. § 112 first paragraph based on the allegation that the claims fail to comply with the written description and enablement requirements.

(4) The fourth and final issue to be reviewed on appeal is the rejection of Claim 1 under 35 U.S.C. § 103(a) in view of U.S. patent no. 6,646,149.

ARGUMENT

Issue #1

This rejection should be reversed for the simple reason that contrary to the position taken by the Office up to this point, the specification provides explicit, literal support for the definitions of the substituents set forth in Claim 1.

In maintaining this rejection, the Office contends that : "the scope of the generic concept to R3 and R4 are both hydrogen *together with the subcombination of Markush elements as now recited in the "currently amended" claim 1* is NEW MATTER." (page 2 of the Office Action mailed December 29, 2004). This conclusion is incorrect because support for Claim 1 finds explicit, literal support on page 11, lines 10-25 reproduced below (emphases added):

> In preferred sulfonyl amino acid derivatives **according to formula I**, **Ar^1 is an unsubstituted or substituted phenyl**, preferably a 4-chlorophenyl group, X is preferably O, R^1, R^2, **R^3 and R^4 are preferably hydrogen**, n is 1, Ar^2 is preferably thienyl, R^5 is H or C_1-C_6-alkyl.
>
> In said preferred embodiment, R^6 is selected from the group comprising or consisting of H, a substituted or unsubstituted C_1-C_6-aliphatic alkyl-e.g. a C_1-C_6-alkylamino aryl, a C_1-C_6-alkylamino heteroaryl, a substituted or unsubstituted cyclic C_4-C_8-alkyl containing optionally 1-3 heteroatoms and being optionally fused with an unsubstiuted or substituted aryl or heteroaryl; or R^6 is an unsubstituted or substituted aryl or heteroaryl.
>
> The above mentioned aryl or heteroaryl groups are optionally substituted by substituted or unsubstituted C_1-C_6-alkyl, like trihalomethyl, substituted or unsubstituted C_1-C_6-alkoxy, substituted or unsubstituted C_2-C_6-alkenyl, substituted or unsubstituted C_2-C_6-alkynyl, amino, acylamino, aminocarbonyl, substituted or unsubstituted C_1-C_6-alkoxycarbonyl, aryl, carboxyl, cyano, halogen, hydroxyl, nitro, acyloxy, sulfoxy, sulfonyl, C_1-C_6-thioalkoxy.

For ease of reference, below is a Table which aligns the substituents set forth in Claim 1 and the above-noted portions of the specification supporting each of these substituents:

CLAIM 1 SUBSTITUENTS	SUPPORTING DISCLOSURE ON PAGE 10
Ar^1 is unsubstituted phenyl or phenyl substituted with one or more substituents selected from the group consisting of . . .	Ar^1 is an unsubstituted or substituted phenyl
Ar^2 is thienyl;	"Ar^2 is preferably thienyl"
X is O;	"X is preferably O"
n is 1;	"n is 1"
R^1, R^2, R^3 and R^4 are hydrogen;	"R^1, R^2, R^3 and R^4 are preferably hydrogen"
R^5 is H or C_1-C_6-alkyl;	"R^5 is H or C_1-C_6-alkyl"
R^6 is selected from the group consisting of H, substituted or unsubstituted C_1-C_6-aliphatic alkyl, and substituted or unsubstituted saturated cyclic C_4-C_8-alkyl optionally containing 1-3 heteroatoms and optionally fused with an unsubstituted or substituted aryl or an heteroaryl; or R^6 is a substituted aryl, unsubstituted aryl, substituted heteroaryl, or unsubstituted heteroaryl,	"R^6 is selected from the group comprising or consisting of H, a substituted or unsubstituted C_1-C_6-aliphatic alkyl-e.g. a C_1-C_6-alkylamino aryl, a C_1-C_6-alkylamino heteroaryl, a substituted or unsubstituted cyclic C_4-C_8-alkyl containing optionally 1-3 heteroatoms and being optionally fused with an unsubstiuted or substituted aryl or heteroaryl; or R^6 is an unsubstituted or substituted aryl or heteroaryl"
wherein said aryl or heteroaryl groups may be substituted with one or more substituents selected from the group consisting of substituted or unsubstituted C_1-C_6-alkyl, trihalomethyl, substituted or unsubstituted C_1-C_6-alkoxy, substituted or unsubstituted C_2-C_6-alkenyl, substituted or unsubstituted C_1-C_6-alkynyl, amino, acylamino, aminocarbonyl, substituted or unsubstituted C_1-C_6-alkoxycarbonyl, aryl, carboxyl, cyano, halogen, hydroxy, nitro, acyloxy, acylamino, sulfoxy, sulfonyl, and C_1-C_6-thioalkoxy.	"The above mentioned aryl or heteroaryl groups are optionally substituted by substituted or unsubstituted C_1-C_6-alkyl, like trihalomethyl, substituted or unsubstituted C_1-C_6-alkoxy, substituted or unsubstituted C_2-C_6-alkenyl, substituted or unsubstituted C_2-C_6-alkynyl, amino, acylamino, aminocarbonyl, substituted or unsubstituted C_1-C_6-alkoxycarbonyl, aryl, carboxyl, cyano, halogen, hydroxyl, nitro, acyloxy, sulfoxy, sulfonyl, C_1-C_6-thioalkoxy."

In view of this explicit, literal support why has this rejection even been raised? It seems that, perhaps, the Office's confusion of this point lies in the disclosure of <u>one</u> embodiment of the compounds of formula 1 on page 10. Illustrative of this is the Office's statements on page 2 of the Office Action of December 29, 2004 pointing to the present

specification on page 10, which states that in one embodiment of the compounds of formula spanning pages 9-10: "at least one of R^3 and/or R^4 must be an amino acid residue." (see also the Office Action mailed December 29, 2004 at page 2).

However, the Office's reliance on the disclosure on page 10 stating that R3 and/ R4 must be an amino acid residue is misplaced. What the Office has failed to appreciate is that the description of R3 and R4 is only **one** embodiment of the compounds of the formula (1), while the compounds defined as a preferred embodiment on page 11 (reproduced above), is another embodiment. In fact, by simply reviewing the disclosure on pages 9 through 12 one can appreciate that there are several embodiments.

Furthermore, there are specific examples provided in the specification that clearly demonstrate that the specification describes compounds within this generic disclosure on page 11. Examples 1, 4 and 6 describe species within the generic disclosure claimed and described hereinabove.

Therefore, the specification clearly provides **explicit, literal support** for the generic formula defined in Claim 1 as one preferred embodiment, which may overlap and/or be separate from other embodiments described in the specification, including those described on pages 9-10.

As this rejection applies to Claim 9 (see page 3 of the Office Action mailed December 29, 2004), the rejection is without merit. When discussing Claim 9 and Claim 1, the Office has stated that "all compounds of claim 9 have an R6 being alkyl substituted with "heteroarylamino" moiety. . . The instantly amended claim 1 is drawn to R6 being substituted C_1-C_6 aliphatic alkyl." This is simply incorrect.

Claim 1 defines R^6 as follows (see Appendix I):

R^6 is selected from the group consisting of

> H, substituted or unsubstituted C_1-C_6-aliphatic alkyl, and substituted or unsubstituted saturated cyclic C_4-C_8-alkyl optionally containing 1-3 heteroatoms and optionally fused with an unsubstituted or substituted aryl or an heteroaryl; or R^6 is a substituted aryl, unsubstituted aryl, substituted heteroaryl, or unsubstituted heteroaryl . . .

The claims clearly include other possible substituents at the R^6 position other than C_{1-6} aliphatic alkyl. The Office purports that the groups available as substituents for the the R^6 position are limited to those listed in the paragraph bridging pages 11-12 of the specification (see Page 3 of the Office Action of December 29, 2004). However, what the Office has failed to appreciate is that this disclosure relates to a subset of embodiments within the general formula I. Alternative embodiments are also disclosed falling within the chosen subsstituents for the R^6 position. In fact, attention is directed to page 7, line 24 to page 8, line 10, reproduced below for reference:

> "Substituted or unsubstituted" : Unless otherwise constrained by the definition of the individual substituent, the above set out groups, like alkyl, heteroaryl, alkenyl, alkynyl and aryl etc. groups can optionally be substituted with from 1 to 5 substituents selected from group consisting of C1-C6-alkyl, acetoxy, alkoxy, alkenyl, alkynyl, amino, aminoacyl, aminocarbonyl, alkoxycarbonyl, aryl, carboxyl, cyano, halogen, hydroxy, nitro, sulfoxy, sulfoxy, thioalkoxy, trihalomethyl and the like.

Thus, it is readily apparent that the rejection as it applies to Claim 9 (and Claim 29, see below) is based on several mistakes. First, the R^6 position is not limited to only substituted C_{1-6} aliphatic alkyl. Second, the possible substituents available at the R^6 position are not limited solely to the one preferred set of embodiments listed on pages 10-11 because the specification provides additional disclosure. Taken together, support for the species listed in Claim 9 (as well as Claim 29) **is** found in the specification and find **proper antecedent** basis in the Claim 1.

There is no question that in view of the above facts, this ground of rejection should be REVERSED.

Issue #2

This issue is an objection under 37 C.F.R. 1.75(c) and is based on the allegation "that the base claim 1 as now amended, reading in light of the specification, does not contain the R6 moieties as found in claim 9, thus, claim 9 is broadening of the base claim." (See page 3 of the Office Action mailed December 29, 2004). Since no further details are provided by the Office, it is difficult to understand the basis for this rejection. Nonetheless, as readily apparent by the comments below, Claims 9 and 29 are properly dependent from Claim 1.

This objection stems from the misunderstanding of what is claimed, i.e., the R_6 substituents. As discussed in detail above, the compounds in Claim 9 and Claim 29 further define the substituents in the compound of formula I. In fact, the R_6 substituents listed in Claim 1 when properly read, i.e., not limited to some of the examples in the specification, encompass the specific R_6 substituent defined by the compounds set forth in Claims 9 and 29 and therefore further limit Claim 1.

There is no question that in view of the above facts, this ground of objection should be REVERSED.

ISSUE # 3

This issue relates to the Office's contention that the specification fails to comply with the written description and enablement requirements. However, as written description is separate and apart from enablement, in the comments below Appellants will explain why all of the pending claims satisfy both of these requirements, addressing each requirement separately.

There are four types of claims in this application: (1) the compound—Claims 1, 7, 8, 9, 29, 39, and 41; (2) processes for preparing the compound—Claims 18 and 19; (3) a composition comprising at least one of the compounds—Claim 17; and (4) methods of using the compounds—Claims 30-38 and 42-45.

For the reasons explained above, the specification unequivocally describes the compounds of formula I (again referring to the text at page 11). The pharmaceutical composition of Claim 17 is described starting on page 12, line 24. Therefore, as this rejection is applied on written description grounds to Claims 1, 7, 8, 9, 17, 29, 39 and 41, the rejection should be reversed.

To the issue of enablement of these claims, i.e., how to make and how to use, the specification at page 13, line 24 – page 14, line 3 the describes how the compounds can be used:

> . . .the compounds pursuant to formula I are useful for the treatment or prevention of immuno- and/or neuronal-related diseases or pathological states in which inhibition of JNK1 and/or JNK2 and/or JNK3 plays a critical role such as epilepsy; neurodegenerative diseases including Alzheimer's disease, Huntington's disease, Parkinson's disease; retinal diseases; spinal cord injury; head trauma, autoimmune diseases including multiple Sclerosis, inflammatory bowel disease (IBD), rheumatoid arthritis; asthma; septic shock; transplant rejection; cancers including breast, colorectal, pancreatic and cardiovascular diseases including stroke, cerebral ischemia, arterosclerosis, myocordial infarction, myocordial reperfusion injury.

Starting on page 15, line 17, the specification describes how to make the compounds of formula I. On page 16, starting at line 1 a detailed preferred method of synthesis is also described. In addition, on pages 26-30, several detailed examples of making compounds of formula I are described. Therefore, the compound claims as well as the pharmaceutical composition containing the same are clearly enabled by the specification.

Furthermore, in light of the fact that the specification on pages 15 and 17 describes the process steps of making compounds of formula I, the methods for preparing the compounds as set forth in Claims 18 and 19 are clearly adequately described by the specification. Still further, in light of the fact that the Applicants have demonstrated that these processes can be used to make compounds within the definition of formula I in the Examples and the Office has not provided any evidence or rationale as to why one would expect these processes not to work, the processes claimed in Claims 18 and 19 are also enabled.

Turning to the methods of using the compounds to (a) treat a disease of the autoimmune and/or neuronal system (e.g., Claim 30), (b) treat cancer (Claim 42), and (c) treat a cardiovascular disease, Appellants submit that the claims are both adequately described and enabled by the specification as originally filed. There are a number of issues raised by the Office in rejecting these claims (page 4 of the Office Action of December 29, 2004): (1) "down regulate or inhibit" allegedly is new matter; and (2) "the method of using the compounds for such an array of enormous utility in treating all autoimmune disease and/or neuronal system is incredible" and "the claims of treating such disorder of the autoimmune and/or neuronal system constitutes 'reach through claims.'" Each of these is discussed separately below.

Claim 33 includes the phrase "to down-regulate or inhibit the JNK pathway." Attention is directed to the specification at page 5, lines 6-10, which states (emphasis added):

> It is notably an objective of the present invention to provide relatively small molecule chemical compounds which are able to modulate, preferably **down-regulate or to inhibit the JNK (Jun Kinase) pathway** so to be available as a convenient method of treating diseases which are preferably mediated by the JNK function.

So how is there no antecedent basis for the phrase found in Claim 33? Clearly, the addition of this phrase into Claim 33 does not constitute new matter as the Office has alleged. Furthermore, the specification on pages 37, 38 and 39 describe *in vivo* test data in mice and gerbils. The resultant observations when tied back to the description of how JNK is involved in these diseases clearly provides a nexus for the phrase found in the claims.

The method of using the compounds to treat a disorder of the autoimmune and/or neuronal system is both described and enabled by the specification.

Attention is directed to the following statements in the specification (emphases added):

> Page 13, line 24 – page 14, line 3: Specifically, **the compounds pursuant to formula I are useful for the treatment or prevention of** immuno- and/or neuronal-related diseases or **pathological states** in which **inhibition of JNK1 and/or JNK2 and/or JNK3 plays a critical role** such as epilepsy; neurodegenerative diseases including Alzheimer's disease, Huntington's disease, Parkinson's disease; retinal diseases; spinal cord injury; head trauma, autoimmune diseases including multiple Sclerosis, inflammatory bowel disease (IBD), rheumatoid arthritis; asthma; septic shock; transplant rejection; **cancers including breast, colorectal, pancreatic** and **cardiovascular diseases including stroke, cerebral ischemia, arterosclerosis, myocordial infarction, myocordial reperfusion injury**.

Here, the specification establishes that the compounds of formula I inhibit JNK and since JNK plays a critical role in a variety of autoimmune and/or neuronal system, one would reasonably conclude that that the compounds can be used to treat a variety of disorders. On page 13, line 3 through page 14, line 14, the specification further elaborates on this point:

> The compounds according to formula I, alone or in the form of a pharmaceutical composition, are useful for the modulation of the JNK pathway, more specifically for treatment or prevention

> of disorders associated with abnormal expression or activity of JNK, notably of JNK1 and/or JNK2 and/or JNK3. . .
>
> Specifically, the compounds pursuant to formula I are useful for the treatment or prevention of immuno- and/or neuronal-related diseases or pathological states in which inhibition of JNK1 and/or JNK2 and/or JNK3 plays a critical role such as . . .
>
> Quite surprisingly, it was now found that sulfonyl amino acid derivatives according to formula I are suitable pharmaceutically active agents, by effectively inhibiting the action of JNKs, notably JNK2 and 3. . .

However, the specification does more than state conclusions. The specification provides clear evidence of the activities of the compounds of formula I. Provided with the nexus discussed above and described in the specification, one of ordinary skill in the art would recognize that the Inventors had possession of the claimed methods. Furthermore, one of ordinary skill in the art could make and/or use the invention as claimed. Specifically, attention is directed to data presented in the specification on pages 32 and 34, portions of which are highlighted and reproduced below for easy reference:

> Page 32, lines 6-17: The activities of the sulfonyl amino acid derivatives according to formula I were assessed using the above described biological assays. Representative values are given in the table shown below:

Example	*JNK3*	*JNK2*	*p38*	*ERK2*
1	1.2	2.7	>30	>30
6	0.64	1.3	>30	>30

> The values indicated in respect of JNK2 and 3, p38 and ERK2 refer to the IC_{50} (μM), i.e. the amount necessary to **achieve 50% inhibition of said target (e.g. JNK2)**. AS# denotes an exemplary test compound as set out with its number in the above examples. From the above table it could be derived that said test compounds according to formula I do have a signifi-cant effect both on JNK2 and 3, but virtually no effect onto p38 and ERK2, thus delivering a **quite selective inhibitory effect**.

> Page 34, lines 26-27 (emphasis added): "The result of this assay shows that various test compounds **decrease the production of IL-2 of more than 30%@3uM.**"

As described in the specification on pages 1-4, JNK (Jun kinase) act by its central involvement in crucial signaling pathways in the cell and as a result is integral to a number of pathways centered on expression genes, maintaining cell viability, and mediating signals from cytokines such as interleukin 2 and interferon. Furthermore, the specification describes that these activities are involved in a number of diseases and therefore by controlling the activity of JNKs one has the tool to treat these different disease states. Other than simply stating conclusions that the claims are "incredible"[1] or "reach through claims"[2] the Office has not provided any evidence or any reasonable basis to contradict what is so well explained in the specification and known by the skilled artisan.

Accordingly and in view of the above, this rejection should be reversed.

[1] Page 4 of the Office Action mailed December 29, 2004.
[2] Page 4 of the Office Action mailed December 29, 2004.

ISSUE #4

Claim 1 is patentable in view of U.S. patent no. 6,646,149 ("U.S. '149") because the generic disclosure of U.S. '149 does not provide any reasonable suggestion for the compounds claimed in Claim 1, the disclosure actually found in U.S. '149 is inapplicable to the compound claimed in Claim 1, and nothing the Office has proffered counters the surprising advantages the specification has described. Further details on these three points follows.

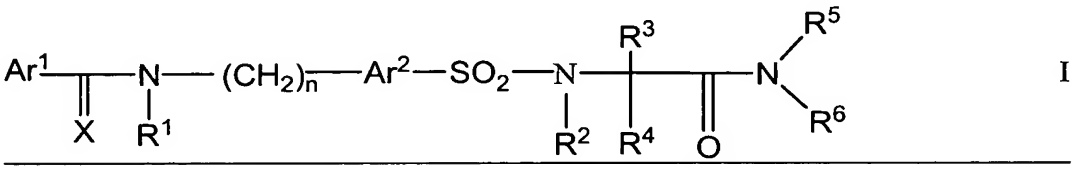
U.S. '149 describes bispolyamines having the general formula set forth in col. 15, lines 40-43. The U.S. '149 specification then goes on to list a laundry list of possible substituents the combinations of which appear to encompass thousands of possible compounds. The Office, citing compounds 1233 and 1241 on sheet 29 of the drawings of U.S. '149 then contends that "the instant claim is merely picking and choosing of a more limited combination of the generically disclosures alternatives by Vermeulin et al. '149." (page 5 of the Office Action). Appellants respectfully disagree.

As discussed throughout the specification of U.S. '149, the only point of the discussion therein is to make and use polyamine compounds and derivatives of polyamines to inhibit polyamine transport and/or polyamine binding proteins. See Abstract and col 1, lines 16-31; col. 6, lines 48-53 ("the present invention is directed to various polyamine analogues and derivatives"); cp;. 7, lines 22-24 ("a polyamine analogue or derivative of the invention includes on that binds to a polyamine-binding site of a molecule and/or inhibits polyamine transport"); and col. 15, lines 40-43: noting the block noted on the right of the formula labeled "polyamine."

The enormous possible number of combinations encompassed by U.S. '149 provides no reasonable suggestion for the compounds as claimed in Claim 1. On this basis alone, the rejection should be REVERSED.

Second, the compounds claimed in Claim 1 and those described in U.S. '149 are fundamentally different. The compounds of U.S. '149 as described in col. 15, lines 31-34 are **polyamine derivatives that are linked together via terminal amino groups** . . . In fact, the compounds cited by the Office for alleged support for the rejection also include polyamine moieties. For ease of reference, attached as evidence and listed in Appendix II is Sheet 29 of 59, Figure 9B(6) of U.S. '149.

In contrast, the compounds defined by formula I do not contain polyamine groups. In the formula I found in Claim 1 (reproduced below for easy reference), following the sulfamide moiety (-SO_2-N-), there is a CH_2 group (noting that R_3 and R_4 are both defined as hydrogen:



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On this basis alone and in combination with the above, this rejection should be REVERSED.

The Examiner's reliance on compounds 1233 and 1241 on sheet 29 of the drawings of U.S. '149 is misplaced. The Examiner contends that the "art clearly taught the variation of a linker chain between the NR2 and the carbonyl moiety and the ordinary skill person was offered the concept of modifying 1233 with 1241 on the same page i.e. establishing a prima facie structural obvious." (page 11 of the Examiner's answer). First, the disclosure of two distinct compounds separate and apart from each other on the same page does nothing to suggest any modification. This simply seems like rationale for an unsubstantiated position.

Third, as explained in the section of this Brief entitled "Summary of Claimed Subject Matter" the specification at page 9 states: "Quite surprisingly, it was now found that sulfonyl amino acid derivatives according to formula I are suitable pharmaceutically active agents, by

effectively inhibiting the action of JNKs, notably JNK2 and 3." This statement is supported by data also discussed above and found in the specification at page 32, lines 6-17; page 34, lines 26-27; page 37, lines 11-12; page 37, lines 24-25; and page 39, lines 4-5.

Accordingly, on this basis alone and in combination with the above points, this rejection should be REVERSED.

CONCLUSION

In view of the above remarks, Appellants request that all of the rejections be REVERSED.

Respectfully submitted,

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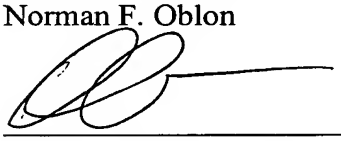

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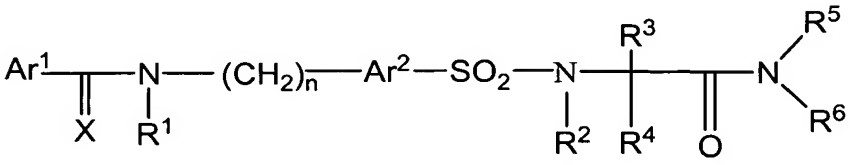
APPENDIX 1 (CLAIMS)

Claim 1 (Previously Presented): A compound according to formula I



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with its geometrical isomers, in an optically active form as enantiomers, diastereomers, as well as in the form of racemates, as well as pharmaceutically acceptable salts thereof, wherein

Ar^1 is unsubstituted phenyl or phenyl substituted with one or more substituents selected from the group consisting of substituted or unsubstituted C_1-C_6-alkyl, trihalomethyl, substituted or unsubstituted C_1-C_6-alkoxy, substituted or unsubstituted C_2-C_6-alkenyl, substituted or unsubstituted C_2-C_6-alkynyl, amino, acylamino, aminocarbonyl, substituted or unsubstituted C_1-C_6-alkoxycarbonyl, aryl, carboxyl, cyano, halogen, hydroxy, nitro, acyloxy, acylamino, sulfoxy, sulfonyl, and substituted or unsubstituted C_1-C_6- thioalkoxy;

Ar^2 is thienyl;

X is O;

n is 1;

R^1, R^2, R^3 and R^4 are hydrogen;

R^5 is H or C_1-C_6-alkyl;

R^6 is selected from the group consisting of H, substituted or unsubstituted C_1-C_6-aliphatic alkyl, and substituted or unsubstituted saturated cyclic C_4-C_8-alkyl optionally containing 1-3 heteroatoms and optionally fused with an unsubstituted or substituted aryl or an heteroaryl; or R^6 is a substituted aryl, unsubstituted aryl, substituted heteroaryl, or unsubstituted heteroaryl,

wherein said aryl or heteroaryl groups may be substituted with one or more substituents selected from the group consisting of substituted or unsubstituted C_1-C_6-alkyl, trihalomethyl, substituted or unsubstituted C_1-C_6-alkoxy, substituted or unsubstituted C_2-C_6-alkenyl, substituted or unsubstituted C_1-C_6-alkynyl, amino, acylamino, aminocarbonyl, substituted or unsubstituted C_1-C_6-alkoxycarbonyl, aryl, carboxyl, cyano, halogen, hydroxy, nitro, acyloxy, acylamino, sulfoxy, sulfonyl, and C_1-C_6-thioalkoxy.

Claims 2-6 (Cancelled).

Claim 7 (Previously Presented): The compound according to claim 1, wherein

R^5 is H; and R^6 is a C_1-C_6-alkyl which is substituted by one or more substituents selected from the group consisting of an aryl, an heteroaryl group, an aminoaryl, aminoheteroaryl, aryloxy, and heteroaryloxy,

wherein said aryl and heteroaryl groups are optionally substituted by substituted or unsubstituted C_1-C_6-alkyl, trihalomethyl, substituted or unsubstituted C_1-C_6-alkoxy, substituted or unsubstituted C_2-C_6-alkenyl, substituted or unsubstituted C_2-C_6-alkynyl, amino, acylamino, aminocarbonyl, substituted or unsubstituted C_1-C_6-alkoxycarbonyl, substituted or unsubstituted aryl, carboxyl, cyano, halogen, hydroxy, nitro, sulfoxy, or C_1-C_6-thioalkoxy.

Claim 8 (Previously Presented): The compound according to claim 7, wherein R^6 is a substituted or unsubstituted pyridyl group.

Claim 9 (Previously Presented): A compound according to claim 1 which is:

4-chloro-N-({5-[({2-[(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]amino}ethyl)-amino]-2-oxoethyl}amino)sulfonyl]thien-2-yl}methyl)benzamide,

4-chloro-N-[(5-{[(2-{[2-({5-nitropyridin-2-yl}amino)ethyl]amino}-2-oxoethyl)-amino]sulfonyl}thien-2-yl)methyl]benzamide,

4-chloro-N-({5-[({2-oxo-2-[(2-{[3-(trifluoromethyl)pyridin-2-yl]amino}ethyl)-amino]ethyl}amino)sulfonyl]thien-2-yl}methyl)benzamide,

4-chloro-N-({5-[({2-oxo-2-[(2-{[5-(trifluoromethyl)pyridin-2-yl]amino}ethyl)-amino]ethyl}amino)sulfonyl]thien-2-yl}methyl)benzamide, or

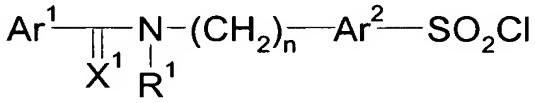
4-chloro-N-[(5-{[(2-oxo-2-{3-[(trifluoromethyl)sulfonyl]anilino}ethyl)amino]-sulfonyl}thien-2-yl)methyl]benzamide.

Claims 10-16 (Cancelled).

Claim 17 (Previously Presented): A pharmaceutical composition comprising at least one compound according to claim 1 and a pharmaceutically acceptable carrier, diluent or excipient.

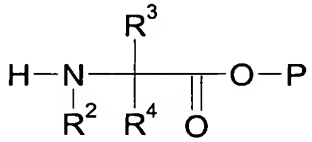
Claim 18 (Previously Presented): A process for the preparation of the compound according to claim 1 comprising:

a) preparing a sulfonyl compound V,



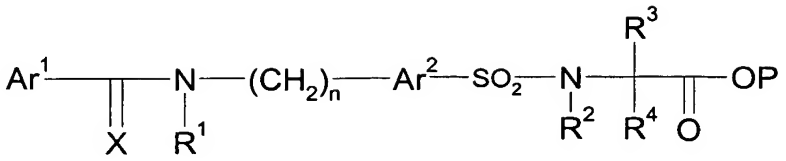
V

b) reacting the sulfonyl compound V with ~~the~~ a protected amino acid compound VIII



VIII

to obtain a compound IX



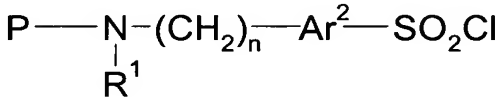
IX

c) deprotecting the compound IX and then

d) coupling with an amine of type R^5R^4NH.

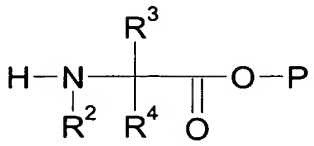
Claim 19 (Previously Presented): A process for the preparation of the compound according to claim 1, comprising:

a) preparing a protected sulfonyl compound VII



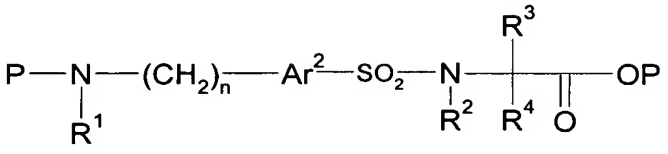
VII

b) reacting the sulfonyl compound VII with a protected amino acid compound VIII



VIII

to obtain a compound X, then



X

e) deprotecting the compound X;

f) coupling with an amine of type R^5R^4NH;

g) deprotecting, and

h) acylating.

Claims 20-28 (Cancelled).

Claim 29 (Previously Presented): The compound according to claim 1, which is 4-chloro-N-({5-[({2-[(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]amino}ethyl)-amino]-2-oxoethyl}amino)sulfonyl]thien-2-yl}methyl)benzamide.

Claim 30 (Previously Presented): A method to treat a disorder of the autoimmune and/or neuronal system comprising

administering the compound of claim 1 to a mammal in need thereof in an amount effective to treat a disorder of the autoimmune and/or neuronal system.

Claim 31 (Previously Presented): The method according to claim 30, wherein the mammal is a human.

Claim 32 (Previously Presented): The method of claim 30, wherein the compound is administered orally.

Claim 33 (Previously Presented): A method to treat a disorder of the autoimmune and/or neuronal system comprising

administering the compound of claim 1 to a human in an amount effective to down-regulate or inhibit the JNK pathway.

Claim 34 (Previously Presented): The method of claim 30, wherein the compound is administered to a human having at least one neuronal disorder selected from the group

consisting of epilepsy, Alzheimer's disease, Huntington's disease, Parkinson's disease, retinal disease, spinal cord injury, and head trauma.

Claim 35 (Previously Presented): The method of claim 30, wherein the compound is administered to a human having at least one autoimmune disease selected from the group consisting of multiple sclerosis, inflammatory bowel disease, rheumatoid arthritis, asthma, septic shock, and transplant rejection.

Claims 36-37 (Canceled).

Claim 38 (Previously Presented): The method of claim 30, wherein the compound is administered in an amount effective for decreasing the production of IL-2.

Claim 39 (Previously Presented): The compound according to claim 1, wherein Ar^1 is a chloro-phenyl group.

Claim 40 (Canceled).

Claim 41 (Previously Presented): The compound according to claim 1, wherein

R^6 is a C_1-C_6-alkyl which is substituted by substituents selected from the group consisting of an aryl, an heteroaryl group, an aminoaryl, aminoheteroaryl, aryloxy, and heteroaryloxy,

wherein said aryl and heteroaryl groups are optionally substituted by substituted or unsubstituted C_1-C_6-alkyl, trihalomethyl, substituted or unsubstituted C_1-C_6-alkoxy, substituted or unsubstituted C_2-C_6-alkenyl, substituted or unsubstituted C_2-C_6-alkynyl, amino,

acylamino, aminocarbonyl, substituted or unsubstituted C_1-C_6-alkoxycarbonyl, substituted or unsubstituted aryl, carboxyl, cyano, halogen, hydroxy, nitro, sulfoxy, or C_1-C_6-thioalkoxy.

Claim 42 (Previously Presented): A method to treat cancer comprising

administering the compound of claim 1 to a mammal in need thereof in an amount effective to treat cancer.

Claim 43 (Previously Presented): The method of claim 42, wherein the compound is administered to a human having breast cancer, colorectal cancer, or pancreatic cancer.

Claim 44 (Previously Presented): A method to treat cardiovascular disease comprising

administering the compound of claim 1 to a mammal in need thereof in an amount effective to treat cardiovascular disease.

Claim 45 (Previously Presented): The method of claim 44, wherein the compound is administered to a human having at least one cardiovascular disease selected from the group consisting of stroke arteriosclerosis, myocardial infarction, and myocardial reperfusion injury.

APPENDIX II (EVIDENCE)

1. U.S. patent no.6,646,149, Figure 9(B)-6, Sheet 29 of 59. Entered in the record on December 29, 2004 by citation in the U.S.P.T.O Office Action of the same date.

RELATED PROCEEDINGS APPENDIX

None.